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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : MARTIN, et al.

U.S. Serial No.: Not Yet Known, corresponding to International Application No. PCT/US03/18716, filed June 13, 2003, which claims priority of U.S. Serial No. 10/172,346, filed June 13, 2002

Filed : Herewith

For : IN-VIVO ENERGY DEPLETING STRATEGIES FOR KILLING DRUG-RESISTANT CANCER CELLS

Law Offices of Albert Wai-Kit Chan, LLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, NY 11357

December 10, 2004

Mail-Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, Applicants would like to direct the Examiner's attention to the following references which are listed below and on Forms PTO/SB/08A and PTO/SB/08B, which are attached hereto as **Exhibit A and Exhibits 1-9.**

1. Herceg Z. & Z.-Q. Wang. Failure of poly(ADP-ribose) polymerase cleavage by caspases leads to induction of necrosis and enhanced apoptosis. Mol. Cell Biol. 19:5124-5133 (1999)
2. Hirsch, T. et al. The apoptosis-necrosis paradox. Apoptogenic proteases activated after mitochondrial permeability transition determine the mode of cell death. Oncogene 15:1573-1581 (1997)

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8. Mehmet, H., et al. Relation of impaired energy metabolism to apoptosis and necrosis following transient cerebral hypoxia-ischaemia. *Cell Death Differ.* 5:321-329 (1998)
9. Nicotera, P. & Leist, M. Energy supply and the shape of death in neurons and lymphoid cells. *Cell Death Differ.* 4:435-442 (1997)
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14. Tsujimoto, Y. Apoptosis and necrosis: intracellular ATP level as a determinant for cell death modes. Cell Death Differ. 4:429-434 (1997)
15. PCT International Search Report for Sloan-Kettering Institute for Cancer Research, et al., Int'l App'l No. PCT/US01/46886, Filed on December 4, 2001, Dated May 22, 2002
16. PCT Written Opinion for Sloan-Kettering Institute for Cancer Research, et al., Int'l App'l No. PCT/US01/46886, Filed on December 4, 2001, Dated April 17, 2003
17. PCT International Preliminary Examination Report for Sloan-Kettering Institute for Cancer Research et al., Int'l App'l No. PCT/US01/46886, Filed December 4, 2001, Dated September 5, 2003.
18. PCT Notification of Transmittal of the International Search Report for Sloan-Kettering Institute for Cancer Research Application No. PCT/US03/18716, Filed on June 13, 2003, Dated November 25, 2003.

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49. Jurkowitz, et al., Adenosine, Inosine, and Guanosine Protect Glial Cells During Glucose Deprivation and Mitochondrial Inhibition: Correlation Between Protection and ATP Preservation. *Journal of Neurochemistry*, 1998, 71(2):535-548. **[Exhibit 1]**

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50. Lieberthal, et al., Graded ATP depletion can cause necrosis or apoptosis of cultured mouse proximal tubular cells. *American Physiological Society*; 1998, F315-F327.
[Exhibit 2]

51. Lu, et al., Cellular ATP Depletion by LY309887 as a Predictor of Growth Inhibition in Human Tumor Cell Lines. *Clinical Cancer Research*; January 1, 2000, 5:271-277.
[Exhibit 3]

52. Venkatachalam, et al., Energy Thresholds That Determine Membrane Integrity and Injury in a Renal Epithelial Cell Line (LLC-PK1). *J. Clin. Invest.*; 1988, 81:745-758.
[Exhibit 4]

53. Anundi, et al., Fructose prevents hypoxic cell death in liver. *The American Journal of Physiology*; 1987, Sep;253(3 Pt 1):G390-G396. [Exhibit 5]

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[Exhibit 6]

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56. PCT International Search Report for Sloan-Kettering Institute for Cancer Research, et al., Int'l App'l No. PCT/US03/18716, Filed on June 13, 2003, Dated November 25, 2003. [Exhibit 8]

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57. WO 93/23014 A1 (Martin et al.) Chemotherapeutic Drug Combinations, Published 25 November 1993 [Exhibit 9]

REMARKS

References 1-14 of the above-identified fifty-seven (57) references were submitted as Information Disclosure Statement to the United States Patent and Trademark Office on December 9, 2002 for U.S. Serial No. 10/172,346, filed June 13, 2002. References 15-16 of the above-identified fifty-seven (57) references were submitted as Supplemental Information Disclosure Statement to the United States Patent and Trademark Office on September 4, 2003 for U.S. Serial No. 10/172,346, filed June 13, 2002. Reference 17 of the above-identified fifty-seven (57) references was submitted as Supplemental Information Disclosure Statement to the United States Patent and Trademark Office on September 19, 2003 for U.S. Serial No. 10/172,346, filed June 13, 2002. Reference 18 of the above-identified fifty-seven (57) references was submitted as Supplemental Information Disclosure Statement to the United States Patent and Trademark Office on December 12, 2003 for U.S. Serial No. 10/172,346, filed June 13, 2002. Also, References 19-48 of the above-identified fifty-seven (57) references were submitted as Supplemental Information Disclosure Statement to the United States Patent and Trademark Office on May 19, 2004 for U.S. Serial No. 10/172,346, filed June 13, 2002. Accordingly, Applicants will not provide these documents unless otherwise requested by the Examiner. References 49-57 of the above-identified fifty-seven (57) references are attached herewith.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

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Respectfully submitted,

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Sheet 1 of 7

Comments if Known

Application Number	Not Yet Known
Filing Date	Herewith
First Named Inventor	Daniel S. MARTIN
Art Unit	Not Yet Known
Examiner Name	Not Yet Known
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FOREIGN PATENT DOCUMENTS

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15	PCT/US01/46886		12-04-2001	Sloan-Kettering Institute for Cancer Research, et al.	PCT International Search Report	
16	PCT/US01/46886		12-04-2001	Sloan-Kettering Institute for Cancer Research, et al.	PCT Written Opinion	
17	PCT/US01/46886		12-04-2001	Sloan-Kettering Institute for Cancer Research, et al.	PCT International Preliminary Examination Report	
18	PCT/US03/18716		06-13-2003	Sloan-Kettering Institute for Cancer Research, et al.	PCT Notification of Transmittal of the International Search Report	
56	PCT/US03/18716		06-13-2003	Sloan-Kettering Institute for Cancer Research, et al.	PCT International Search Report	
57	WO 93/23014 A1		11-25-2003	Sloan-Kettering Institute for Cancer Research, et al.	PCT Published Application	

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	1	Herceg Z. & Z.-Q. Wang. Failure of poly(ADP-ribose) polymerase cleavage by caspases leads to induction of necrosis and enhanced apoptosis. Mol. Cell Biol. 19:5124-5133 (1999)		
	2	Hirsch, T. et al. The apoptosis-necrosis paradox. Apoptogenic proteases activated after mitochondrial permeability transition determine the mode of cell death. Oncogene 15:1573-1581 (1997)		
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	11	Nord, L.D., et al. Apoptosis induced in advanced CD8F1-murine mammary tumors by the combination of PALA, MMPR and 6AN precedes tumor regression and is preceded by ATP depletion. <i>Canc. Chemo. Pharm.</i> 40:376-384 (1997)	
	12	Sane, A.-T. & Bertrand, R. Caspase inhibition in camptothecin-treated U-937 cells is coupled with a shift from apoptosis to transient G1 arrest followed by necrotic cell death. <i>Canc. Res.</i> 59:3565-3569 (1999)	
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	22	Kemeny, N., Schneider, A., Martin D.S., Colofiore J., Sawyer, R.C., Derby, S., Salvia, B., Phase I trial of N-phosphonacetyl-L-aspartate, methotrexate, and 5-fluorouracil with leucovorin rescue in patients with advanced cancer. <i>Cancer Res.</i> ; 1989, 49(16): 4636-4639.	
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	24	Koutcher, J.A., Alfieri, A.A., Matie, C., Meyer, K.L., Street, J.C., Martin, D.S., Effect of 6-aminonicotinamide on the pentose phosphate pathway: 31P NMR and tumor growth delay studies. <i>Magn. Reson. Med.</i> , 1996, 36(6):887-892.	

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		Application Number	Not Yet Known
		Filing Date	Herewith
		First Named Inventor	Daniel S. MARTIN
		Art Unit	Not Yet Known
		Examiner Name	Not Yet Known
Sheet	4	of	7
		Attorney Docket Number	
		636-C-PCT-US	

OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS

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	25	Koutcher, J.A., Alfieri, A.A., Tsai, J.C., Matei, C., Stolfi, R.L., Ballon, D., Martin, D.S., Evaluation of chemotherapy and radiation enhancement and 31P NMR spectral changes induced by biochemical modulation. <i>Cancer Invest.</i> , 1997, 15(2):111-120.
	26	Koutcher, J.A., Alfieri, A.A., Thaler, H., Matei, C., Martin, D.S., Radiation enhancement by biochemical modulation and 5-fluorouracil. <i>Int. J. Rad. Oncol.</i> ; 1997, 39(5):1145-1152.
	27	Mahmood, U., Street, J.C., Matei, C., Ballon, D., Martin, D.S., Koutcher J.A., In vivo detection by 31P NMR of pentose phosphate pathway block secondary to biochemical modulation. <i>NMR Biomed.</i> ; 1996, 9(3):114-120.
	28	Martin DS, Kemeny NE. 1992. Modulation of fluorouracil by N-phosphonacetyl-L-aspartate: a review. <i>Semin. Oncol.</i> ; 19(2 Suppl 3):49-55.
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	30	Martin, D.S., Stolfi, R.L., Colofiore, J.R., Nord, L.D., Sternberg, S., Biochemical modulation of tumor cell energy in vivo: II. A lower dose of Adriamycin is required and a greater antitumor activity is induced when cellular energy is depressed. <i>Cancer Invest.</i> ; 1994, 12(3):296-307.
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	32	Martin, D.S., Schwartz, G.K., Chemotherapeutically induced DNA damage, ATP depletion, and the apoptotic biochemical cascade. <i>Oncol. Res.</i> ; 1997, 9(1):1-5
	33	Martin, D.S., Spriggs, D., Koutcher, J.A., A concomitant ATP-depleting strategy markedly enhances anticancer agent activity. <i>Apoptosis</i> ; 2001, 6:125-131, 2001.
	34	Martin, D.S. Purine and pyrimidine biochemistry, and some relevant clinical and preclinical cancer chemotherapy research In: G. Powis and R.A. Prough (eds), <i>Metabolism and Action of Anti-Cancer Drugs</i> , 91-140. London, Taylor and Francis, 1987.

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	35	Martin, D.S., Stolfi, R.L., Sawyer, R.C., Spiegelman, S. Casper, E.S. and Young, C.W. Therapeutic utility of utilizing low doses of N-(phosphonacetyl)L-aspartic acid in combination with 5-flourouracil; a murine study with clinical relevance. <i>Cancer Res.</i> 43:2317-2321, 1983.		T ²
	36	Martin, D.S., Alfieri, A., Koutcher, J.A., et al., Selective-killing of drug-resistant mammary carcinomas by exploiting the tumor cell ATP-viability threshold. <i>Proc. AACR</i> 45:570 (Abstract 2462), 2004.		
	37	Martin, D.S., Stolfi, R.L., Colofiore, J.C., Koutcher, J.A., Alfieri, A., Sternberg, S., and Nord, L.D. Apoptosis resulting from anti-cancer agent activity in vivo is enhanced by biochemical modulation of tumor cell energy. In: M. Lavin and D. Walters (eds.) <i>Programmed Cell Death. The Cellular and Molecular Biology of Apoptosis</i> 279-296, New York: Harwood Academic 1993.		
	38	Martin, D.S., Stolfi, R.L., Nord, L.D. and Colofiore, J.R. Enhancement of chemotherapeutically-induced apoptosis in vivo by biochemical modulation of poly-(ADP-ribose) polymerase. <i>Oncol. Rep.</i> 3:317-322, 1996.		
	39	Martin, D.S. Cancer chemotherapy: past is prologue. <i>Mt. Sinai. J. Med.</i> 52:426-434, 1985.		
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	41	Koutcher, J.A., Alfieri, A., Stolfi, R.L., Devitt, M.L., Colofiore, J.R., Nord, L.D., and Martin, D.S. Potentiation of three drug chemotherapy regimen by radiation. <i>Cancer Res.</i> 53:3518-3823, 1993.		
	42	Colofiore, J.R., Stolfi, R.L., Nord, L.D., and Martin, D.S. On the relationship of ATP-depletion to chemotherapeutically-induced tumor regression. <i>Int. J. Oncol.</i> 7:1401-1404, 1995.		
	43	Nord, L.D. Stolfi, R.L., Colofiore, J.R., Martin, D.S., Correlation of retetinotin of tumore methylmercaptopurine riboside-5'-phosphate with effectiveness in CD8F1 murine mammary tumor regression. <i>Biochem Pharmacol.</i> 1996, 51(5):621-627.		
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		Filing Date	Herewith	
		First Named Inventor	Daniel S. MARTIN	
		Art Unit	Not Yet Known	
		Examiner Name	Not Yet Known	
Sheet 6	of 7	Attorney Docket Number	636-C-PCT-US	

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	45	O'Dwyer, P.J., Judes, G.R., Colofiore, J., Walczak, J., Hoffman, J., LaCreta F.P., Comis, R.L., Martin, D.S., Ozols, R.F., Phase I trial of fluorouracil modulation by of N-phosphonacetyl-L-aspartate and 6-methylmercaptopurine riboside: optimization of 6-methylmercaptopurine riboside dose and schedule through biochemical analysis of sequential tumor biopsy specimens. <i>J. Natl. Cancer Inst.</i> ; 1991, 83(17):1235-1240.		T ²
	46	Stolfi, R.L., Martin, D.S., Enhancement of anticancer activity by selective inhibition of rapidly proliferating tissues of the host. <i>Pharmacol. Ther.</i> ; 1991, 49(1-2):43-54.		
	47	Stolfi, R.L., Colofiore, J.R., Nord, L.D., Koutcher, J.A., Martin, D.S., Biochemical modulation of tumor cell energy: regression of advanced spontaneous murine breast tumors with a 5-fluorouracil-containing drug combination. <i>Cancer Res.</i> ; 1992, 52(15):4074-4081.		
	48	Stolfi, R.L., Colofiore, J.R., Nord, L.D., Martin, D.S., Enhanced antitumor activity of an Adriamycin + 5-fluorouracil combination when preceded by biochemical modulation. <i>Anticancer Drugs</i> ; 1996, 7(1):100-104.		
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	50	Lieberthal, et al., Graded ATP depletion can cause necrosis or apoptosis of cultured mouse proximal tubular cells. <i>American Physiological Society</i> ; 1998, F315-F327.		
	51	Lu, et al., Cellular ATP Depletion by LY309887 as a Predictor of Growth Inhibition in Human Tumor Cell Lines. <i>Clinical Cancer Research</i> ; January 1, 2000, 5:271-277.		
	52	Venkatachalam, et al., Energy Thresholds That Determine Membrane Integrity and Injury in a Renal Epithelial Cell Line (LLC-PK1). <i>J. Clin. Invest.</i> ; 1988, 81:745-758.		
	53	Anundi, et al., Fructose prevents hypoxic cell death in liver. <i>The American Journal of Physiology</i> ; 1987, Sep;253(3 Pt 1):G390-G396.		
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	55	Yager, et al., Correlation between Content of High-Energy Phosphates and Phypoxic-Ischemic Damage in Immature and Mature Astrocytes. Elsevier Science Publishers, Amsterdam; 1994, 82(1-2):62-68.	

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